A Practical and Enantiospecific Synthesis of (−)-(*R*)- and (+)-(*S*)-Piperidin-3-ols

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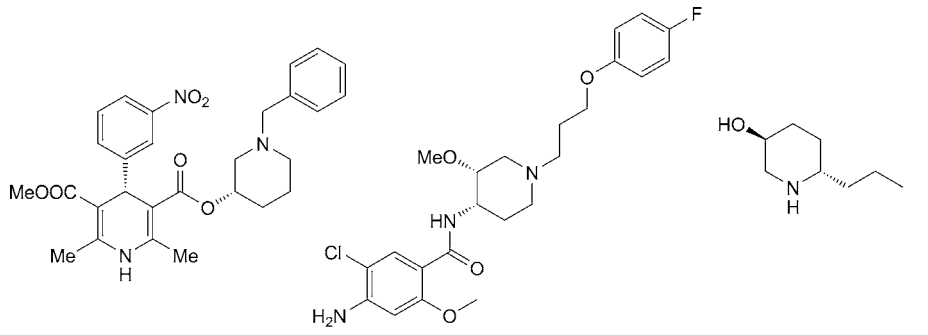
A highly enantiospecific, azide-free synthesis of (−)-(*R*)- and (+)-(*S*)-piperidin-3-ol in excellent yield was developed. The key step of the synthesis involves the enantiospecific ring openings of enantiomerically pure (*R*)- and (*S*)-2-(oxiran-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-diones with the diethyl malonate anion and subsequent decarboxylation.

Introduction. – Natural products often inspire for synthetic organic chemists, because of their biological properties and complex structural design, and they 'catalyze' the development of new methodologies in organic synthesis. In the majority of natural products, the so-called privileged skeletal fragments can be identified. One of the important classes of skeletal frameworks present in diverse array of biologically active natural and unnatural products are chiral piperidin-3-ols [1]. Benidipine (**1**) [2a], cisapride (**2**) [2b], and pseudoconhydrine (**3**) [3] are some of the important biologically active compounds which possess piperidin-3-ol moieties in their structures (*Fig. 1*). Benidipine hydrochloride is used as calcium channel blocker, whereas cisapride is a gastroprokinetic agent. Pseudoconhydrine is found in hemlock, a poisonous herb of the parsley family. Other medicinally important compounds containing optically active piperidin-3-ols in their skeletal frameworks include cassine [4], deoxocassine fraction



Benidipine (**1**) Cisapride (**2**) Pseudoconhydrine (**3**)

Fig. 1. *Enantiomerically pure piperidin-3-ol-containing natural products*

[5], Bao Gong Teng A [6], cholinotoxic agents [7], 2,3-oxydosqualene cyclase inhibitors [8], and nootropics or antiarrhythmic agents [9].

There are several approaches reported for the synthesis of racemic piperidin-3-ols. Metal-catalyzed high-pressure hydrogenation of pyridin-3-ol [10], ring expansion of aziridinium ion with aq. NaOH [11], thermal rearrangement [12], and *Diels–Alder* reactions [13] are some of the key methodologies employed. The enantiospecific synthesis of (−)-(*R*)- and (+)-(*S*)-piperidin-3-ols have been reported starting from optically pure(−)-D-mannitol [14], (*S*)-malic acid, and L-(+)-glutamic acid [15], *etc.*; however, yields of the isolated products were rather poor, or potentially unsafe or hazardous reagents were used. *Cossy et al.* reported a highly enantiospecific synthesis of (−)-(*R*)-*N*-alkylpiperidin-3-ols from optically pure 2-(hydroxymethyl)-*N*-alkylpyrrolidines by ring expansion [16]. The chiral resolution of racemic piperidin-3-ols was accomplished with optically active acids [17] and also by an enzymatic process [18]. As a part of our ongoing research on biologically active natural products [19], herein we describe the enantiospecific synthesis of both (−)-(*R*)- and (+)-(*S*)-piperidin-3-ols with high optical purity.

Results and Discussion. – Our strategy for an efficient enantiospecific synthesis of *tert*-butyl (−)-(3*R*)-3-hydroxypiperidine-1-carboxylate (**4a**) is outlined in *Scheme 1*.

Reduction of enantiomerically pure (5*R*)-5-hydroxypiperidin-2-one (**5a**) would be one of the most promising approaches for the synthesis of the protected (−)-(*R*)-piperidin-3-ol **4a**. In turn, **5a** could be obtained by the deprotection of (*R*)-2-[(5-oxotetrahydrofuran-2-yl)methyl]-1*H*-isoindoline-1,3(2*H*)-dione (**6a**) with appropriate reagents. The latter could be prepared by a sequential reaction, involving the enantiospecific epoxide opening of (*S*)-2-(oxiran-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-dione (**7a**) with diethyl malonate (**8**), lactonization, followed by ester hydrolysis and decarboxylation. The reaction of (+)-(*S*)-epichlorohydrin **9a** with phthalimide (**10**) would generate *N*-[(oxiran-2-yl)methyl]phtalimide **7a** (*Scheme 1*).

For the synthesis of **7**, **7a**, and **7b**, we have modified the procedure developed by *Alcántara* and co-workers [20a], and as a model reaction, racemic epichlorohydrin **9**

Scheme 1. *Retrosynthetic Analysis for* **4a**

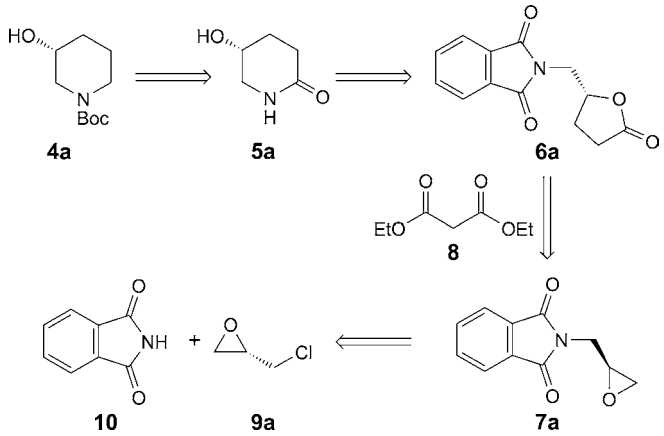
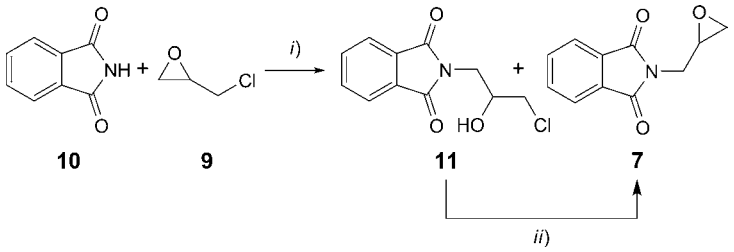


Table 1. *Epoxide Ring-Opening with Phthalimide Promoted by Al_2O_3/*N*-Methylpyrrolidin-2-one* (NMP)[a])



Entry	Epoxide	**11** [% area]	Product **7**	**7**	
				Area [%]	ee [%]
1	*rac*-Epichlorohydrin (**9**)	82	**7**	16	0
2	(*S*)-Epichlorohydrin (**9a**)	86	**7a**	12	98.6
3	(*R*)-Epichlorohydrin (**9b**)	84	**7b**	14	90.8

[a]) *i*) Basic Al_2O_3, NMP, 64–68°, 40–45 h, then THF, HCl gas. *ii*) K_2CO_3, toluene, reflux 35–40 h; overall yield 62%.

was reacted with **10** using basic Al_2O_3 in NMP (*Table 1*). The reaction gave two products, the chlorohydrin **11** and the (oxiranyl)methyl derivative **7** in a ratio of 82 : 16. The crude mixture was then subjected to the epoxidation reaction with K_2CO_3/toluene to yield **7** as the sole product; however, the reaction did not proceed to completion, and *ca.* 5% of unidentified impurities formed along with **7**. To circumvent this impurity formation, the crude mixture containing **11** and **7** was first fully converted to **11** by purging HCl gas into a dilute solution of **11** and **7** in THF, and further cyclization was performed with K_2CO_3/toluene. In this way, we could isolate pure **7** in 62% overall yield. After optimization of the reaction conditions, the enantiomerically pure epichlorohydrins **9a** and **9b**, respectively, were reacted with phthalimide, and (oxiranyl)methyl-phtalimides **7a** and **7b** were isolated in excellent yields. The enantiomeric purity of **7b** was comparatively low, as the enantiomeric purity of the (*R*)-epichlorohydrin used for the reaction was low (94%).

Then, **7a** was subjected to an enantiospecific ring-opening reaction with the anion of diethyl malonate (**8**) in EtOH and gave **12a**. During the pH adjustment of the reaction mixture with aq. 5N HCl, **12a** was hydrolyzed to the corresponding carboxylic acid. From the mixture, EtOH and H_2O were evaporated under reduced pressure, and the crude compound was subjected to decarboxylation in DMSO in the presence of *in-situ* generated NaCl. The (−)-2-[(2*R*)-(5-oxotetrahydrofuran-2-yl)methyl]-1*H*-isoindoline-1,3(2*H*)-dione (**6a**) thus was obtained in 52% yield. The novel compound **6a** exhibited an optical purity of 100% by 'chiral HPLC' with an $[\alpha]_D$ value of −67.28 ($c = 0.647$, $CHCl_3$). Additional structural evidence was obtained by single-crystal X-ray-analysis of **6a** (*Fig. 2*)[1]). These studies clearly established that the ring-expansion reaction

[1]) The crystal data have been deposited with the *Cambridge Crystallographic Data Centre* under the deposition No. CCDC-906722.

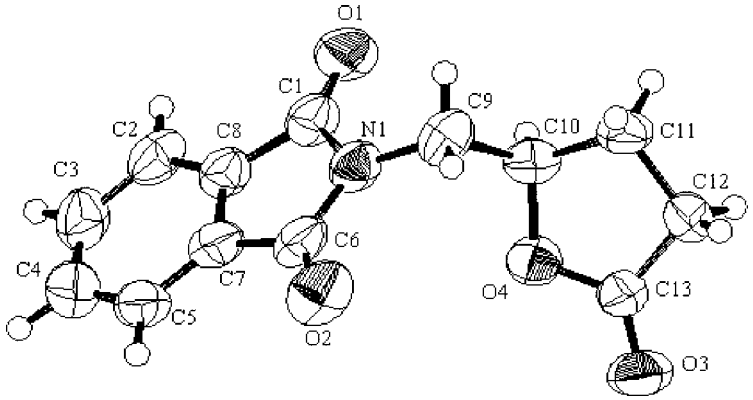
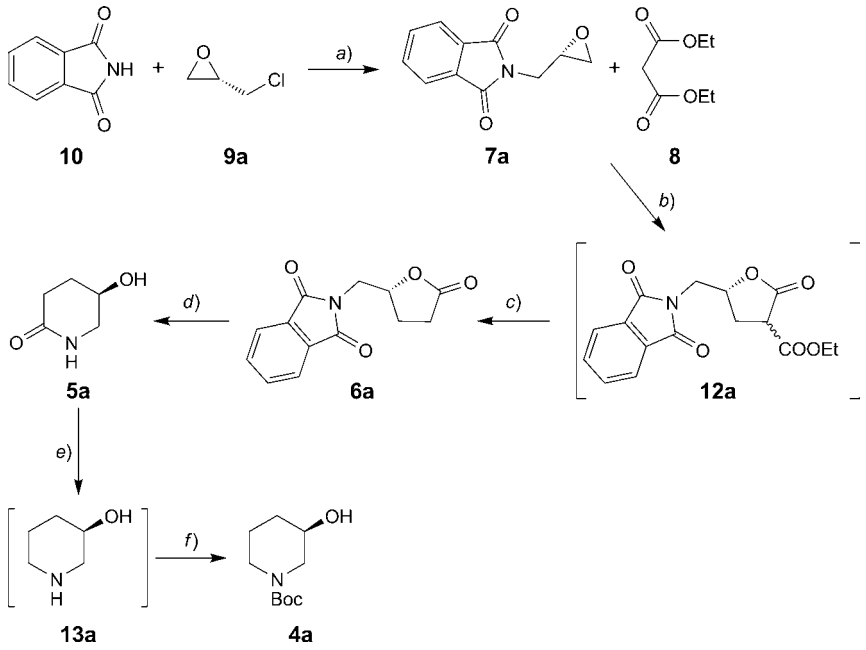


Fig. 2. *ORTEP Diagram of (–)-2-{[(2*R*)-5-oxotetrahydrofuran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione* (**6a**)

proceeded *via* a highly enantiospecific ring opening of **7a** by the anion of **8** with high regiospecificity.

Scheme 2. *Synthesis of* tert*-Butyl (–)-(3*R*)-3-Hydroxypiperidine-1-carboxylate* (**4a**)



a) 1. Basic Al_2O_3, NMP, 64–68°, 40–45 h, then THF, HCl gas, 2. K_2CO_3, toluene, reflux 35–40 h; overall yield 62%. *b*) EtOH, THF, Na, 10–20°, and 25–35°, 15 h. *c*) Aq. 5M HCl, DMSO, 125–130°, 15–20 h (*b* and *c* two-step overall yield, 52%). *d*) $MeNH_2/H_2O$, MeOH, 50–60°, 18–20 h (yield 77%), or aq. NH_3 (28% soln.), 3–4 h (yield 68%). *e*) $LiAlH_4$, THF, reflux, 30–40 h. *f*) $NaHCO_3$, Et_3N, CH_2Cl_2, Boc_2O, H_2O, r.t., 2–3 h, two-steps overall yield 61%.

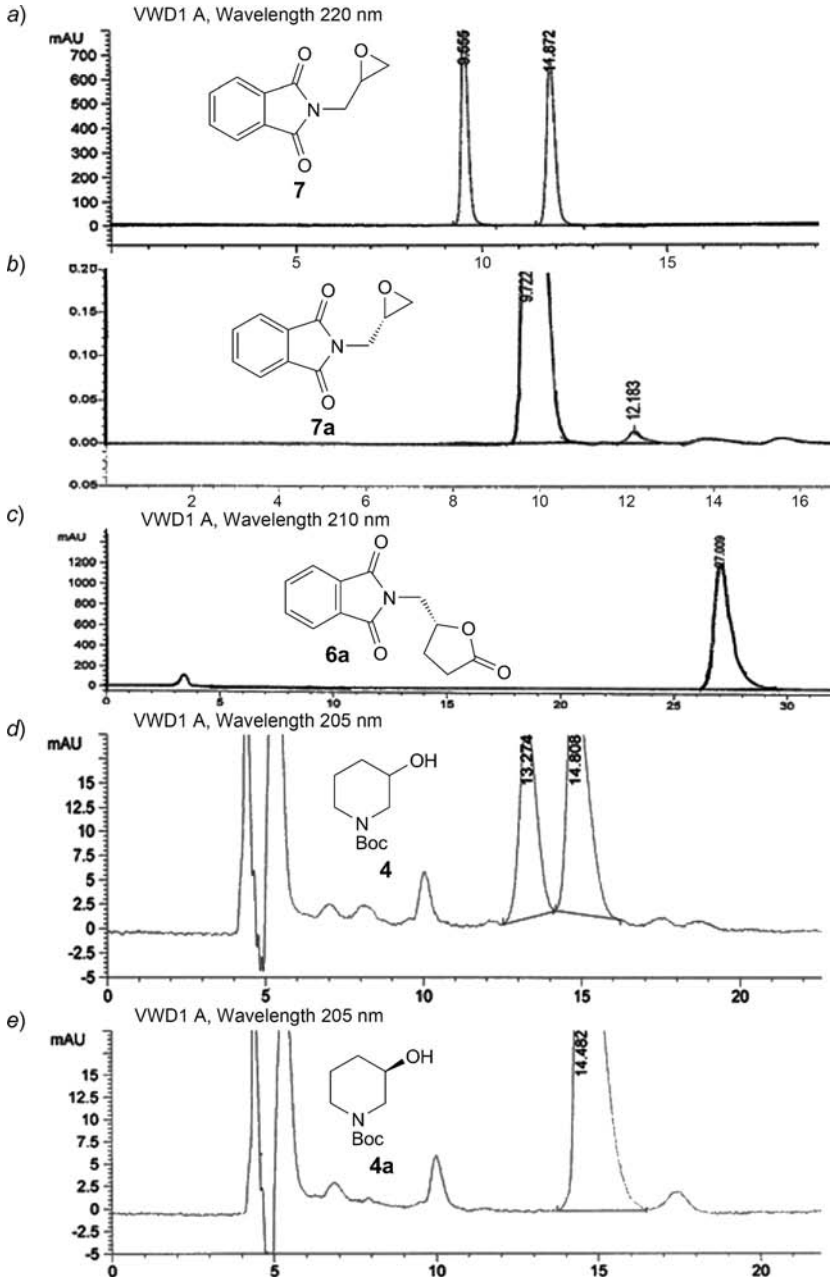


Fig. 3. *'Chiral HPLC' of compounds* **7**, **7a**, **6a**, **4**, *and* **4a**. *a*) HPLC of racemic 2-(oxiran-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-dione (**7**). *b*) HPLC of (+)-2-[(2*S*)-oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (**7a**); *Chiralpak-1A* (250 × 4.6 mm, 5.0 μm), mobile phase, hexane/^{i}PrOH 80 : 20. *c*) HPLC of (−)-2-{[(2*R*)-5-oxotetrahydrofuran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (**6a**; *Chiralpak-1A* (250 × 4.6 mm, 5.0 μm); mobile phase, hexane/^{i}PrOH: 80 : 20. *d*) HPLC of racemic *tert*-butyl 3-hydroxypiperidine-1-carboxylate (**4**). *e*) HPLC of *tert*-butyl (−)-(3*R*)-3-hydroxypiperidine-1-carboxylate (**4a**; *Chiralcel OC* (250 × 4.6 mm, 5.0 μm); mobile phase; hexane/^{i}PrOH 95 : 05.

Then, **6a** was subjected to deprotection of phthalimide using an aqueous solution of $MeNH_2$. After the completion of the reaction, N^1,N^2-dimethylphthalamide was removed by concentration of the reaction mixture, followed by dilution with EtOH. The crude **5a** [7b] was isolated after concentration of the EtOH filtrate under reduced pressure, and was further purified by recrystallization from a mixture MeOH/Et_2O. The (+)-(5*R*)-5-hydroxypiperidin-2-one (**5a**) thus obtained was converted to **13a** by reduction with $LiAlH_4$ [7b][14], and further *N*-Boc protection afforded *tert*-butyl (−)-(3*R*)-3-hydroxypiperidine-1-carboxylate (**4a**) [21] in 61% overall yield with an ee of 100% (*Scheme 2*). The optical purity of all the substrates and intermediates were determined by 'chiral HPLC' methods (*Fig. 3*). The specific rotation of all the isolated intermediates, **7a**, **7b**, **6a**, **6b**, **5a**, **5b**, **4a**, and **4b**, where studied in detail and compared with the reported values (*Table 2*).

The enantiomer *tert*-butyl (+)-(3*S*)-3-hydroxypiperidine-1-carboxylate (**4b**) was also synthesized starting from (−)-(*R*)-epichlorohydrin (**9b**) in an identical way. The optical purities of **4a** and **4b** were based on the optical purity of the starting epichlorohydrin **9a** and **9b**, and there was no racemization observed during the entire course of these synthetic transformations.

Table 2. *Enantiomeric Purity* (HPLC) *and Specific Optical Rotations* (*SOR*) *of Compounds* **7a**, **6a**, **5a**, **4a**, **7b**, **6b**, **5b**, *and* **4b**[a])

Compound	Enantiomeric purity/ee	SOR $[\alpha]_D$	M.p. [°]
7a	99.3/98.6	9.26 ($c = 2.24$, $CHCl_3$) [20b]	101–103
6a	100/100	−67.28 ($c = 0.647$, $CHCl_3$)	120–122
5a	–	9.8 ($c = 0.50$, MeOH)	122–124
4a	100/100	−18.92 ($c = 0.122$, EtOH)	Low-melting solid
7b	95.42/90.8	−9.09 ($c = 2.24$, $CHCl_3$) [20b]	102–103
6b	93.3/86.6	63.57 ($c = 0.637$, $CHCl_3$)	121–123
5b	–	−11.87 ($c = 0.648$, MeOH)	114–116
4b	94.4/88.8	19.37 ($c = 0.653$, EtOH) [21b]	Low-melting solid

[a]) For the structures of the compounds, see *Table 1* and *Scheme 2*.

The authors would like to thank *Dr. Reddy's Laboratories* for the permission to carry out this work. We also acknowledge the Analytical Department for providing the analytical support.

Experimental Part

General. All reagents were used as received from commercial sources without further purification, or prepared as described in the literature. TLC plates were visualized by UV light or by treatment with a spray of *Pancaldi* reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O). Chromatographic purification of products was carried out by flash column chromatography (FCC) on silica gel (SiO_2; 60–120 mesh). M.p.: either on *DSC-60A*, *Schimadzu*, or on an *Electro Thermal* melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1650 Fourier*-transform spectrometer. NMR Spectra: *Varian Gemini 400 FT and 500 FT* spectrometers; in $CDCl_3$ and (D_6)DMSO; TMS as internal standard, chemical shifts (δ) in ppm, and coupling constants (J) in Hz. MS: *HP-5989A* quadrapole mass spectrometer. Enantiomeric purities were determined by 'chiral HPLC' with *Chiralpak-1A* and *Chiralcel OC* columns.

*General Procedure for the Synthesis of 2-(Oxiran-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-dione* (**7**). A round-bottom flask was charged with phthalimide (**10**; 50 g, 0.34 mol), racemic epichlorohydrin (**9**;

62.7 g, 0.68 mol), basic Al_2O_3 (15 g), and NMP (50 ml). The mixture was heated to 64–68° and maintained for 40–45 h. Then, the mixture was diluted with THF and purged with dry HCl gas for 30 min, and filtered through *Celite* pad. The filtrate was treated with H_2O, extracted with 2 × 200 ml of AcOEt, and concentrated to dryness under the reduced pressure to afford chlorohydrin **11**. Then, **11** was dissolved in toluene and taken in a round-bottom flask. To the soln. was added dry K_2CO_3 (52.4 g, 0.38 mol), the mixture was heated to reflux for 35–40 h, filtered, and the filtrate was evaporated to dryness under reduced pressure to yield **7** in an overall yield of 62%.

*(+)-2-[(2*S*)-Oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione* (**7a**). From **9a**. Crystaline solid. M.p. 101–103°. $[\alpha]_D^{25} = 9.26$ ($c = 2.24$, $CHCl_3$); [20b]: $[\alpha]_D^{26} = 9.00$ ($c = 2.2$, $CHCl_3$). IR (KBr): 3461, 3006, 1770, 1714, 1398, 1041, 910, 724. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.86 (*dd*, *J* = 3.0, 2.4, 2 H); 7.75 (*dd*, *J* = 3.2, 2.4, 2 H); 3.95 (*dd*, *J* = 5.2, 9.2, 1 H); 3.83 (*dd*, *J* = 5.2, 9.2, 1 H); 3.26–3.23 (*m*, 1 H); 2.81 (*t*, *J* = 4.4, 1 H); 2.69 (*t*, *J* = 2.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.8; 134.0; 131.7; 123.2; 48.9; 45.9; 39.5. HR-EI-MS: 204.0657 (M^+, $C_{11}H_{10}NO_3^+$; calc. 204.0661). 'Chiral HPLC': 99.32% (*S*) and 0.68% (*R*).

*(−)-2-[(2*R*)-Oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione* (**7b**). From **9b**. Crystalline solid. M.p. 102–103°. $[\alpha]_D^{25} = -9.09$ ($c = 2.24$, $CHCl_3$); [20b]: $[\alpha]_D^{26} = -9.00$ ($c = 2.2$, $CHCl_3$). IR (KBr): 3460, 3007, 1769, 1713, 1396, 1308, 1049, 961, 724. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.88 (*dd*, *J* = 3.0, 2.4, 2 H); 7.75 (*dd*, *J* = 3.2, 2.4, 2 H); 3.97 (*dd*, *J* = 5.4, 9.2, 1 H); 3.82 (*dd*, *J* = 5.4, 9.2, 1 H); 3.26–3.24 (*m*, 1 H); 2.81 (*dd*, *J* = 4.8, 4, 1 H); 2.70 (*dd*, *J* = 2.4, 2.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.8; 134.0; 131.7; 123.2; 48.9; 45.9; 39.5. HR-EI-MS: 204.0660 (M^+, $C_{11}H_{10}NO_3^+$; calc. 204.0661). 'Chiral HPLC': 4.58% (*S*) and 95.42% (*R*).

'*Chiral HPLC*' *Method for* **7a** and **7b**. Column, *chiralpak-1A* (250 × 4.6 mm, 5.0 μm); mobile phase, hexane/^{i}PrOH: 80:20; flow rate, 1.0 ml/min; wavelength, 220 nm; column temp., ambient, injection vol, 5 μl; runtime, 25 min; diluent, mobile phase; and conc., 0.5 mg/ml.

*Synthesis of (−)-2-{[(2*R*)-5-Oxotetrahydrofuran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione* (**6a**). In a round-bottom flask, a freshly prepared soln. of EtONa in EtOH (activated Na (6.5 g, 0.282 mol) and 100.0 ml of EtOH) was taken under N_2. *Diethyl malonate* (**8**; 48.0 g 0.299 mol) and anh. THF (30 ml) were added at 25–35°, and then **7a** (20.0 g, 0.0984 mol) was added in portions at 10–20° in 20 min. The mixture was allowed to reach at 25–35° and was stirred at that temp., until the starting material was consumed (monitoring by TLC). The pH of the mixture was carefully adjusted to 5 with 5N HCl. Solvents were evaporated under reduced pressure, and the white suspension of **12a** thus obtained was heated with 120.0 ml of DMSO to 130° and maintained at that temp. until the disappearce of the starting material (TLC). The mixture was then cooled to 25–35° and poured into ice-cold H_2O, the product was extracted with 2 × 200 ml of AcOEt, and the combined org. layers were washed with H_2O (200 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to furnish a crude product (16.2 g), which, upon CC purification (AcOEt/hexane (30% AcOEt)), yielded **6a** (12.5 g, 51.7%). Off-white crystalline solid. Single crystals were generated by slow evaporation of a dil. $CHCl_3$ soln. of **6a** [23]. M.p. 120–122°. $[\alpha]_D^{25} = -67.2$ ($c = 0.64$, $CHCl_3$). IR (KBr): 3471, 2932, 1787, 1764, 1716, 1464, 1430, 1391, 1187, 1034, 722. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.87 (*dd*, *J* = 2.8, 2.8, 2 arom. H); 7.75 (*dd*, *J* = 3.0, 2.4, 2 arom. H); 4.87 (*p*, 1 H); 4.01 (*dd*, *J* = 7.2, 6.0, 1 H); 3.82 (*dd*, *J* = 5.8, 8.8, 1 H); 2.68–2.51 (*m*, 2 H); 2.43–2.34 (*m*, 1 H); 2.17–2.01 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 176.5; 167.6; 134.5; 131.4; 123.1; 76.9; 27.7; 24.8. MS: 246.30 ($[M+1]^+$), 268.30 ($[M+Na]^+$). HR-EI-MS: 246.0762 (M^+, $C_{13}H_{12}NO_4^+$; calc. 246.0766). 'Chiral HPLC': 100% (*R*).

*(+)-2-{[(2*S*)-5-Oxotetrahydrofuran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione* (**6b**). Crystalline solid. M.p. 121–123°. $[\alpha]_D^{25} = 63.57$ ($c = 0.637$, $CHCl_3$). IR (KBr): 3471, 2932, 1787, 1764, 1716, 1464, 1430, 1391, 1187, 1034, 722. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.87 (*dd*, *J* = 2.8, 2.8, 2 arom. H); 7.75 (*dd*, *J* = 3.0, 2.4, 2 arom. H); 4.87 (*p*, 1 H); 4.01 (*dd*, *J* = 7.2, 6.2, 1 H); 3.82 (*dd*, *J* = 5.6, 8.8, 1 H); 2.68–2.51 (*m*, 2 H); 2.43–2.34 (*m*, 1 H); 2.10–2.01 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 176.5; 167.6; 134.5; 131.4; 123.1; 76.9; 27.7; 24.8. MS: 246.10 ($[M+1]^+$), 268.00 ($[M+Na]^+$). HR-EI-MS: 246.0765 (M^+, $C_{13}H_{12}NO_4^+$; calc. 246.0766). 'Chiral HPLC': 93.3% (*S*) and 6.7% (*R*).

'Chiral HPLC' Method for **6a** *and* **6b**. Column, *Chiralpak-1A* (250 × 4.6 mm, 5.0 μm); mobile phase, hexane/^{i}PrOH 80:20; flow rate, 1.0 ml/min; wavelength, 220 nm; column temp., ambient; injection volume, 5 μl; runtime, 25 min; diluent, mobile phase; and conc., 0.5 mg/ml.

*Synthesis of (+)-(5*R*)-5-Hydroxypiperidin-2-one* (**5a**). A round-bottom flask was charged with **6a** (5.0g, 0.0203 mol), 50 ml of MeOH, and 50 ml of $MeNH_2$(40% aq. soln.) and heated to 50–60°. The mixture was maintained at 50–60°, until the starting material disappeared (TLC). Then the mixture was evaporated under reduced pressure at 70–75°. EtOH was added and the mixture was stirred for 2–4 h, the precipitated N^1,N^2-dimethylphthalamide was filtered off. The mother liquor was evaporated under reduced pressure to yield crude **5a**, which upon CC (CH_2Cl_2/MeOH mixture (8% MeOH)) yielded a syrupy mass, which was further purified with using MeOH and Et_2O. The crude was taken in MeOH and heated to 45–55°, then Et_2O was added to the mixture at 20–25°. The product crystallized was filtered off, and wet cake was dried under reduced pressure and afforded **5a** (1.9 g 77%). Crystalline solid. M.p. 121–123°. $[\alpha]_D^{25} = 9.8$ ($c = 0.65$, MeOH); [7b]: $[\alpha]_D^{24} = 13.3$ ($c = 0.5$, MeOH). IR (KBr): 3279, 3195, 2961, 2921, 1707, 1637, 1496, 1407, 1362, 1336, 1265, 1089, 944, 915, 775. ^{1}H-NMR (400 MHz, D_2O (4.6 ref.)): 4.01 (br. *s*, 1 H); 3.31 (*dd*, $J = 3.2, 9.6$, 1 H); 3.05 (*dd*, $J = 4.2, 8.8$, 1 H); 2.18–2.34 (*m*, 2 H); 1.72–1.82 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.9; 63.7; 49.0; 28.0; 27.7. MS: 116.10 ($[M+1]^+$), 138.10 ($[M+Na]^+$). HR-EI-MS: 116.0707 (M^+, $C_5H_{10}NO_2^+$; calc. 116.0712).

*(−)-(5*S*)-5-Hydroxypiperidin-2-one* (**5b**). Crystalline solid. M.p. 114–116°. $[\alpha]_D^{25} = -11.87$ ($c = 0.5$, MeOH); [7b]: $[\alpha]_D^{24} = -12.4$ ($c = 0.5$, MeOH). IR (KBr): 3413, 2921, 1707, 1644, 1407, 1384, 1265, 1093, 915, 773, 568. ^{1}H-NMR (400 MHz, D_2O (4.6 ref.)): 4.01 (br. *s*, 1 H); 3.29 (*dd*, $J = 3.2, 9.6$, 1 H); 3.06 (*dd*, $J = 4.2, 8.8$, 1 H); 2.14–2.33 (*m*, 2 H); 1.71–1.81 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.5; 64.9; 50.1; 29.0; 28.9. MS: 116.10 ($[M+1]^+$), 138.00 ($[M+Na]^+$). HR-EI-MS: 116.0707 (M^+, $C_5H_{10}NO_2^+$; calc. 116.0712).

Synthesis of tert-*Butyl (−)-(3*R*)-3-Hydroxypiperidine-1-carboxylate* (**4a**). A round-bottom flask was charged with $LiAlH_4$ (3.5 g, 0.0921 mol) and anh. THF (25.0 ml) under N_2. To the mixture was added a suspension of **5a** (2.0 g, 0.0173 mol) in THF (25.0 ml) at 0–10° under N_2. The mixture was then stirred at 25–35° for 15 min, and it was further heated to 60–65° for 30–40 h (TLC). The mixture was then cooled to −10°, and a minimum amount of 0.1 M NaOH soln., followed by MeOH, was slowly added. The inorg. salts that were obtained were filtered, and the filtrate was dried (Na_2SO_4), and solvents were evaporated to dryness under reduced pressure and afforded an oily *liquid (*R*)-piperidin-3-ol* (**13a**).

A round-bottom flask charged with obtained **13a** and then diluted with H_2O (5.0 ml). To the mixture were added $NaHCO_3$ (2.90 g, 0.0346 mol), Et_3N (5.24 g, 0.0519 mol), and CH_2Cl_2 (30 ml) at 25–35°. Then, di-(*tert*-butyl) dicarbonate (7.58 g, 0.0347 mol) at 25–35° was added dropwise, and the mixture was stirred for 10–12 h (TLC). It was then diluted with H_2O (15 ml) and stirred for 10 min. The CH_2Cl_2 layer was separated and aq. layer was again extracted with CH_2Cl_2 (10 ml), and the org. layers were combined. The CH_2Cl_2 layer was washed with 10% aq. citric acid soln. (15 ml), followed by 5% aq. $NaHCO_3$ soln. (15 ml) and H_2O (20 ml). The org. layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residue purified by CC to afford **4a** (2.1 g, 61%). Viscous liquid. $[\alpha]_D^{25} = -18.9$ ($c = 0.122$, EtOH). [21c]: $[\alpha]_D^{20} = -10.8$ ($c = 1.1$, $CHCl_3$). IR (Neat): 3412, 3007, 2939, 2862, 1673, 1428, 1366, 1270, 1238, 1173, 1150, 1069, 769. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.73 (*d*, $J = 10.4$, 2 H); 3.50 (br. *s*, 1 H); 3.11 (*ddd*, $J = 8.8, 8.0, 8.8$, 2 H); 1.86 (*d*, $J = 6$, 1 H); 1.71–1.79 (*m*, 2 H); 1.56–1.47 (*m*, 1 H); 1.46 (*s*, 9 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 155.2; 79.6; 66.2; 50.6; 43.9; 32.5; 28.4; 22.3. MS: 224.20 ($[M+Na]^+$). HR-EI-MS: 202.1451 (M^+, $C_{10}H_{20}NO_3^+$; calc. 202.1443). 'Chiral HPLC': 0.12% (*S*), 99.88% (*R*).

tert-*Butyl (+)-(3*S*)-3-Hydroxypiperidine-1-carboxylate* (**4b**). Viscous liquid. $[\alpha]_D^{25} = 19.37$ ($c = 0.65$, EtOH). [21b]: $[\alpha]_D^{25} = 23.8$ ($c = 0.65$, EtOH). IR (neat): 3418, 3007, 2938, 2861, 2127, 1673, 1470, 1428, 1366, 1271, 1173, 1150, 1069, 969, 880, 756. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.73 (*d*, $J = 10.4$, 2 H); 3.50 (br. *s*, 1 H); 3.12 (*ddd*, $J = 8.8, 8.0, 8.8$, 2 H); 1.86 (*d*, $J = 5.6$, 1 H); 1.72–1.79 (*m*, 2 H); 1.54–1.49 (*m*, 1 H); 1.45 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 155.2; 79.7; 66.0; 50.5; 44.3; 32.4; 28.3; 22.6. MS: 224.20 ($[M+Na]^+$). HR-EI-MS: 202.1447 (M^+, $C_{10}H_{20}NO_3^+$, calc. 202.1443).'Chiral HPLC': 94.4% (*S*), 5.57% (*R*).

'Chiral HPLC' Method for **4a** *and* **4b**. Column, *Chiralcel OC* (250 × 4.6 mm, 5.0 μm); mobile phase, hexane/^{i}PrOH 95 : 05; flow rate, 0.8 ml/min; wavelength, 205 nm; column temp., ambient; and injection volume, 5 μl; run time, 25 min; diluent, mobile phase; and conc., 5.0 mg/ml.

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